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Aminolysis of allyl esters with bislithium aryl amides

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Abstract—The aminolysis of allyl esters with bislithium amides is reported. Tertiary aryl amides were synthesized in a one-pot reaction with bislithium amides and a suitable electrophile in good yields. The scope of this reaction was demonstrated with a variety of anilines and aminopyridines and applied to the synthesis of triphenylmethylacetamides.

Several reactions are known for the aminolysis of simple alkyl esters.[1] Due to their stability, alkyl esters are not commonly used in the synthesis of amides and extreme conditions are often required to convert unactivated esters directly to amides.[2] A convenient and mild synthesis of *sec*-amides from methyl and ethyl esters using dilithium amides has been reported by Maruoka and co-workers.[3]

We have used the method employed by Maruoka on amino acid derivatives en route to bicyclic cyclopropylamines.[4] In our synthesis, a tertiary amide (**3**) was required and prepared by reaction of the secondary amide (**2**) with sodium hydride and methyl iodide. (Fig. 1) We discovered that quenching the aminolysis reaction with methyl iodide provided *N*,*N*-4-methoxyphenyl methyl amide (**3a**) directly from the methyl ester in good yield. In a similar fashion, *N*,*N*-4-methoxyphenyl benzyl amide (**3b**) was also prepared. This one-pot reaction gives the tertiary amide in comparable yields as the two-step protocol.

The robust allyl ester is often used as a protecting group in peptide synthesis because it can be removed mildly and selectively with a Pd(0) catalyst.[5] The resulting acid is then free to undergo further modification. There are very few examples, however, of direct aminolysis of allyl esters, the exception being the Staudinger ligation.[6] We attempted to convert an allyl ester directly to an aromatic amide as this procedure would eliminate several

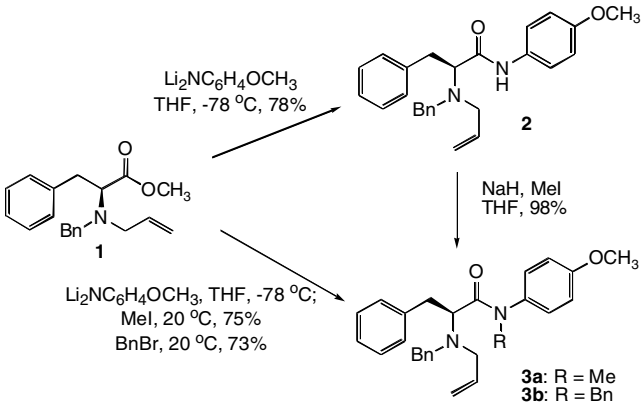

Figure 1. Tertiary amide synthesis.

steps in our synthesis. Application of the conditions reported by Maruoka to *N*,*N*-diallyl phenylalanine allyl ester (**4**) resulted in aminolysis of the ester in poor yield, but with recovery of starting material. When the temperature was raised from −78 °C to 20 °C over several hours, the *sec*-amide product (**5**) was isolated in 79% yield (Fig. 2). Similarly to the phenylalanine methyl ester, the *tert*-amide (**6**) could be obtained in one step in comparable yield.

We confirmed the scope of this reaction with various anilines (Table 1).[17] The reaction is unaffected by the electronic properties of the anilines, but yields decrease when the substituents are incompatible with butyl lithium (entry 5). Additionally, benzyl benzoate (entry 18) underwent facile aminolysis with anisidine and we predict that benzyl esters will react with a variety of aromatic amines with the same success.

Keywords: Aromatic amide; Allyl ester aminolysis; Triphenylmethyl amide.
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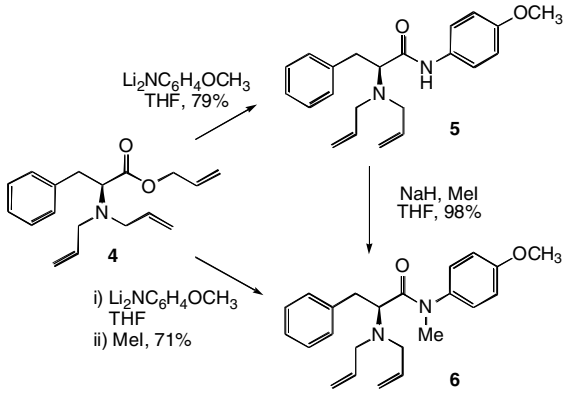

Figure 2. Synthesis of an amide from phenylalanine allyl ester.

In the presence of a ketone moiety, insertion of a butyl group occurs (entries 11 and 12).[18] When a less nucleophilic lithium base is used, aminolysis proceeds with retention of the ketone (Fig. 3). Use of lithium diisopropyl amine results in 58% yield and recovery of the starting ester.

We also found, in agreement with Maruoka's results, that aminolysis of allyl benzoate with a monolithium amide gave a low yield (19%).

Aminopyridines, which are poor nucleophiles, also afforded good yields (entries 13–17). We were concerned that the aminopyridine product could undergo *ortho*-lithiation.[7] Though we did not see evidence of side reactions, we attempted to trap any possible lithiated intermediate to confirm our assumption that pyridyl benzamide was not reacting further. When the aminolysis was complete, as shown by TLC, chlorotrimethylsilane was added to the reaction, but no silylated product was isolated. We are, therefore, confident that no unwanted lithiation occurs.

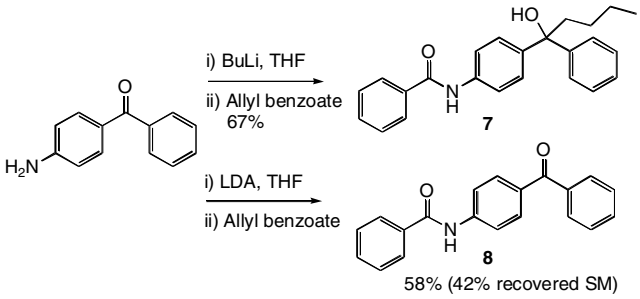

Figure 3. Aminolysis in the presence of a ketone.

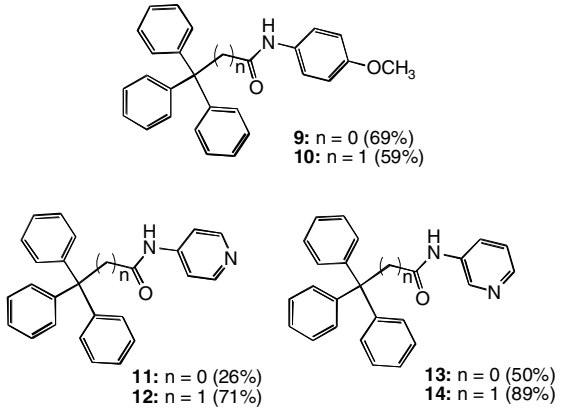

Figure 4. Triphenylmethylamides (yield from methyl ester).

This reaction was applied to methyl and allyl esters of triphenylacetic acid and triphenylpropionic acid. Figure 4 shows some of the synthesized compounds. Amides **9**, **10**, and **11** were first made by Hergenrother and co-workers as part of a library of compounds targeted to induce apoptosis in melanoma cells.[19] Although conversion of the triphenylacetic and propionic acid

Table 1. Products of aminolysis

Entry	Ester	Amine	Product	Yield (%)	Mp (lit.) °C
1	Allyl benzoate	Aniline	*N*-Phenylbenzamide	93	162–164 (163)[8]
2		Anisidine	*N*-(4-Methoxyphenyl)benzamide	93	134–135 (153–155)[9]
3[a]		Anisidine	*N*-(4-Methoxyphenyl)-*N*-methylbenzamide	92	
4		3,5-Dimethoxyaniline	*N*-(3,5-Dimethoxyphenyl)benzamide	65	89–90 (143–145)[10]
5		4-Nitroaniline	*N*-(4-Nitrophenyl)benzamide	21	175–179 (197–198)[11]
6[b]		4-Aminophenol	*N*-(4-Hydroxyphenyl)benzamide	62	214–216 (216)[12]
7[b]		3-Aminophenol	*N*-(3-Hydroxyphenyl)benzamide	71	167–169 (173)[8]
8[b]		2-Aminophenol	*N*-(2-Hydroxyphenyl)benzamide	58	168–169 (168)
9		4-Fluoroaniline	*N*-(4-Fluorophenyl)benzamide	71	175–177 (184–185)[13]
10		2,4-Dichloroaniline	*N*-(2,4-Dichlorophenyl) benzamide	74	111–113 (115)[14]
11		2-Aminobenzophenone	*N*-[2-(1-Hydroxy-1-phenylpentyl)phenyl]-benzamide	79	142–145
12		4-Aminobenzophenone	*N*-[4-(1-Hydroxy-1-phenylpentyl)-phenyl]-benzamide (**7**)	67	110–112
13		4-Aminopyridine	*N*-Pyridin-4-ylbenzamide	86	205–207 (210–211)[7]
14		3-Aminopyridine	*N*-Pyridin-3-ylbenzamide	70	113–115 (118)[15]
15		2-Aminopyridine	*N*-Pyridin-2-ylbenzamide	84	81–83 (82–84)[7]
16		2-Amino-5-chloropyridine	*N*-(4-Chloropyridin-2-yl)benzamide	69	122–123
17		3-Amino-2-chloropyridine	*N*-(2-Chloropyridin-3-yl)benzamide	43	82–83 (89–90)[16]
18	Benzyl benzoate	Anisidine	*N*-(4-Methoxyphenyl)benzamide	77	

[a] 3 Equiv of methyl iodide were added and the reaction stirred for 3 h at room temperature.
[b] Additional equivalents (3.3) of butyl lithium were used.

chlorides to the triphenylmethyl amides worked well in most cases, it failed with several aminopyridines (**12**–**14**). The bislithium amide of 3-amino- and 4-aminopyridine succeeded in preparing these triphenylmethyl amides in good yield. Accordingly, tertiary amides were also produced (approx. 35% yield). The ease of synthesis of these amides illustrates the value of this methodology.

In conclusion, the synthetic utility of bislithium amides was extended to include the aminolysis of allyl and benzyl esters. We have also demonstrated a facile, one-pot synthesis of tertiary aromatic amides from unactivated esters.

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Supplementary data

Experimental procedures and spectroscopic data for all compounds are available. The supplementary data associated with this article are available online in Science Direct, at doi:10.1016/j.tetlet.2006.07.136.

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